COX-2 inhibitor lumiracoxib (400 mg once daily [od]) has comparable efficacy to indomethacin (50 mg three times daily [tid]) for the treatment of acute flares of gout. Secondary analysis of safety and tolerability included a specific, pre-defined comparison of differences in blood pressure.
Methods: This was a 1-week, multicentre, randomized, double-blind, double-dummy, active-controlled, parallel-group study of lumiracoxib 400 mg od (n=118) vs indomethacin 50 mg tid (n=117) (safety population) in patients with acute flares of gout. The primary analysis was a test of non-inferiority in the per protocol population of the mean change from baseline in pain intensity in the study joint over Days 2-5.
The blood pressure profile was assessed by a pre-defined analysis of the mean change from baseline for systolic and diastolic blood pressure.
Results: In the per protocol population, lumiracoxib 400 mg od (n=112) was non-inferior to indomethacin 50 mg tid (n=110). Least square mean (LSM) change from baseline in pain intensity for lumiracoxib was 1.29 (1.47) vs 1.29 (1.50) over Days 2-5 (Days 2-7) treatment period for lumiracoxib and indomethacin, respectively. Both drugs were also comparable in all secondary efficacy assessments.
50% of the patients had a medical history of hypertension. The table below shows the mean change from baseline in BP for lumiracoxib vs indomethacin at study end, after 7 days of treatment (safety population*).

Mean change/(SD)	Lumiracoxib 400 mg od n=114	Indomethacin 50 mg tid n=116	Two sided T-test p-value
Systolic blood pressure (mmHg)	-1.0 (9.74)	2.5 (10.68)	0.009
Diastolic blood pressure (mmHg)	-1.3 (6.06)	0.5 (6.57)	0.028

*Only patients with BP measurement at both baseline and study end were included.

None of the patients in the lumiracoxib group showed a clinically relevant increase in blood pressure (defined as change from baseline of at least 25%), as compared to 1.7% of patients in the indomethacin group.
Only 1.7% of the patients on lumiracoxib 400 mg od discontinued study drug compared with 8.5% on indomethacin 50 mg tid. AEs were reported in 10.2% of patients in the lumiracoxib group compared with 22.2% of patients in the indomethacin group. Due to suspected Good Clinical Practice non-compliance, a post-hoc sensitivity analysis was performed after database closure excluding a center containing 8 patients. The sensitivity analysis revealed no substantial change of the study results, the only exception was diastolic blood pressure (p=0.057).
Conclusions: Lumiracoxib 400 mg od is effective in the treatment of acute gout with efficacy comparable to indomethacin 50 mg tid. In addition, even after short-term treatment, lumiracoxib shows a favourable blood pressure profile as compared to indomethacin, and with fewer AEs and discontinuations. Lumiracoxib may thus provide an alternative effective treatment option for acute gout.

References

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THE ASSOCIATION BETWEEN ECTOPIC BONE FORMATION AFTER HIP REPLACEMENT SURGERY AND CLINICAL OUTCOMES. RESULTS FROM THE HIPAID CLINICAL TRIAL

M. Fransen
The HIPAID Collaborative Group; The George Institute, Camperdown Sydney, Australia

Purpose: To determine if there is an association between the severity of ectopic bone formation after hip replacement surgery, chronic hip pain and physical disability.
Methods: HIPAID was a double-blind randomised placebo-controlled clinical trial conducted in 20 orthopaedic surgery centres in Australia and New Zealand.
902 patients undergoing elective primary or revision total hip replacement surgery were randomly allocated to 14 days treatment with ibuprofen (1200mg daily) or matching placebo commenced within 24 hours of surgery. Participants were required to have hip radiographs, complete self-reported questionnaires measuring of pain and physical function (WOMAC), report analgesia use and undergo several physical performance measures (hip flexion, up and go, 50ft walk time) six to twelve months after surgery.
Results: Hip radiographs were obtained from 798 (88%) participants and scored for ectopic bone formation severity using the Brooker grading (0-4). Among the 294 (37%) of HIPAID participants with radiographic evidence of ectopic bone formation, 108 (37%) had at least moderate severity (Brooker grade 2, 3 or 4). Brooker grade 3 and 4 demonstrated increased pain and function scores, compared with less severe grades of ectopic bone formation; however this trend was not significant. There were was also a trend in the physical performance measures, but again this trend was not significant.

Ectopic bone formation and clinical outcomes

Brooker Grade	Pain (0-10) mean (sd)	Function (0-10) mean (sd)
0	0.97 (1.47)	1.56 (1.57)
1	0.99 (1.49)	1.43 (1.57)
2	0.97 (1.57)	1.87 (1.79)
3 and 4	1.25 (1.85)	2.23 (1.95)

Conclusions: These data, from the largest-ever trial of prophylaxis against ectopic bone formation, suggest that only a small proportion of patients undergoing elective hip replacement surgery will develop clinically relevant ectopic bone around the new hip implant.

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NON-ANIMAL STABILIZED HYALURONIC ACID FOR KNEE OSTEOARTHRITIS: COMBINED ANALYSIS OF TWO PLACEBO-CONTROLLED TRIALS

R. Altman[1], C. Åkermark[2], N. Arden[3]
[1]UCLA, Agua Dulce, CA, [2]Ortopediska Huset, Stockholm, Sweden, [3]MRC Epidemiology Resource Centre, Southampton, United Kingdom

Purpose: With the increased controversy associated with long-term use of NSAIDs and COX-2 inhibitors, there is renewed interest in the use of intraarticular (IA) injections, including hyaluronans (HA), for the management of patients with knee osteoarthritis (OA). Non-animal stabilized hyaluronic acid (NASHA; Durolane®) is administered as a single IA injection for OA of the knee, and has an extended IA residence time (half-life: 4

weeks). In uncontrolled studies, single-injection NASHA was well tolerated and provided significant pain relief for ≥6 months. The results of two randomized, placebo-controlled trials were combined to examine NASHA versus placebo in a pre-defined effectiveness population (EP), which included all randomized, treated patients with OA confined to the knee and without effusion.

Methods: We combined data from two double-blind, randomized trials comparing a single IA injection of NASHA (3 ml, 60 mg) with 3 ml of IA saline. All patients had knee OA by ACR classification criteria. Study 1 lasted for 6 months and study 2 for 6 weeks. Study 2 included only patients with unilateral knee OA. Patients with joint effusion at the time of treatment were excluded from the combined analysis, as effusion may attenuate the benefit of HA through a combination of dilution and increased degradation. The primary efficacy endpoint for the combined analysis was the responder rate at 6 weeks, defined as the percentage of patients with ≥40% reduction in pain and an absolute reduction of ≥5 in WOMAC (Likert) pain score. Responder rates for WOMAC physical function score were calculated (improvements of 20%, 30% and 40% at week 6 *vs* baseline). The analysis was performed using the intention-to-treat population.

Results: The EP comprised a total of 284 patients (NASHA, n=151; placebo, n=133). At 6 weeks, the responder rate was significantly greater with NASHA than placebo group (last observation carried forward: 43.0% *vs* 24.8%, p=0.0013). In study 1, reduction in pain ($p<0.0001$ *vs* baseline) persisted throughout the 6-month follow-up period. The percentage of patients in the EP showing an improvement of ≥1 in global status at 6 weeks was 37.7% in the NASHA group, versus 27.1% for placebo (p=0.0556). For WOMAC physical function, the 20% responder rate was significantly higher with NASHA versus placebo (62.3% *vs* 50.4%, p=0.0439), with a trend in favour of NASHA for the other two criteria. The percentage of patients reporting ≥1 adverse event (AE) was 45.2% with NASHA and 43.3% with placebo. There were no inflammatory reactions and no treatment-related serious AEs.

Conclusions: In an analysis of two placebo-controlled trials, NASHA provided significant reduction in pain versus placebo at 6 weeks post-injection, with persistent pain relief in patients followed for 6 months. These outcomes are similar to those reported for other IA HA preparations, but NASHA has the added benefits of no animal peptide contaminants and a single-injection regimen. NASHA was well tolerated, with no treatment-related serious AEs.

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REGENERATION OF ARTICULAR CARTILAGE AFTER PELVIC OSTEOTOMY IN OSTEOARTHRITIS HIPS DUE TO ACETABULAR DYSPLASIA

S. Jingushi, Y. Noguchi, E. Suenaga, Y. Iwamoto
Kyushu University, Fukuoka, Japan

Purpose: Biomechanical abnormality in the joint is one of the major causes for osteoarthritis. Abnormally large pressure on joints and joint instability will result in degeneration of the articular cartilage followed by joint destruction and deformity. Osteotomy has been carried out to restore such biomechanical abnormality. The main purpose is to prevent osteoarthritis deterioration. In hip joints, osteoarthritis often occurs due to acetabular dysplasia. In order to restore the acetabular dysplasia, periacetabular osteotomy is carried out. The clinical outcomes are reported to be optimal. Additionally, a few case reports showed that osteotomy could result in not only prevention of osteoarthritis deterioration but also regeneration of the injured articular cartilage. In this study, regeneration of articular cartilage was investigated in the osteoarthritis hips due to acetabular dysplasia using arthroscopy before and after osteotomy.

Methods: All the twenty seven hips, that had an operation to remove the metal ware after pelvic osteotomy since January in 1999 till May in 2000, were investigated. Two, twenty, and five hips were at pre-osteoarthritis stage, at early stage and at advanced stage, respectively, when the hips had pelvic osteotomy. The mean age at the operation for metal ware removal was 44 (20-55) years. The mean period since the pelvic osteotomy till the operation for the metal ware removal was 18 (11-60) months. Degeneration of the articular cartilage was evaluated using arthroscopy during the operation for metal ware removal, and the arthroscopic observation was compared with that just before the pelvic osteotomy. Degeneration of acetabular and femoral head cartilage was classified into four grades by allotting a respective 0 to 3 points (degenerative score): grade 0, no degeneration; grade 1, color change, softening, fine irregularity; grade 2, fibrillation, erosion, and grade 3, subchondral bone exposure. The articular cartilage in the weight-bearing area was divided into three 45 degrees ranges; antero-superior (AS), superior (SU), and postero-superior (PS). Additionally for arthroscopic observation at the operation for metal ware removal, it was assessed as grade 2.5 when regeneration articular cartilage was observed, but subchondral bone exposure was remained. Regeneration score was calculated as follows; (degradation score at the operation for metal ware removal) - (degradation score before the pelvic osteotomy).

Results: The mean total degeneration score in all the six lesions of acetabular and femoral head cartilage before pelvic osteotomy and at the operation for metal ware removal was 11.7 (0-18) and 9.6 (0-17), respectively. The mean total regeneration score was 2.1 (-2 -6). Subchondral bone exposure was observed before the pelvic osteotomy in 78%, 70%, and 33% in the AS, SU and PS lesion of the acetabulum cartilage, and in 48%, 33%, and 7% of the femoral head cartilage. In such lesions where subchondral bone exposure was observed before the pelvic osteotomy, the mean ratio of the lesions, where regeneration of the articular cartilage was observed, was 85 (74-100) % (Table 1).

Conclusions: The degeneration scores decreased significantly a few years after pelvic osteotomy indicating that the osteotomy caused regeneration of articular cartilage. In the most lesions where the subchondral bone was exposed, cartilage regeneration was observed. Pelvic osteotomy may switch the articular cartilage metabolism to be from osteoarthritis deterioration mode to regeneration mode. Pelvic osteotomy resulted in not only osteoarthritis deterioration but also regeneration of the articular cartilage.

P365 – Table 1. Regeneration score at the site where subchondral bone was exposed before osteotomy

Regeneration score	Acetabular cartilage (% in parenthesis)			Femoral head cartilage (% in parenthesis)		
	AS	SU	PS	AS	SU	PS
Total number	21	19	9	13	9	2
2	0 (0)	0 (0)	0 (0)	2 (15)	1 (11)	0 (0)
1	11 (52)	9 (49)	4 (44)	4 (31)	4 (44)	1 (50)
0.5	6 (29)	5 (26)	4 (44)	4 (31)	3 (33)	1 (50)
0	4 (19)	5 (26)	1 (11)	3 (23)	1 (11)	0 (0)